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McCune-Albright Syndrome: Growth Hormone Dynamics in Pregnancy

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ABSTRACT

Excess GH secretion has a well recognized association with McCune-Albright syndrome. Although there have been a number of reported pregnancies in uncontrolled acromegaly, none has been described in the McCune-Albright syndrome. We have studied the GH and insulin-like growth factor I (IGF-I) profiles in a patient with confirmed McCune-Albright syndrome and GH hypersecretion throughout a successful pregnancy and postpartum period.

Prepregnancy, IGF-I was 60.6 nmol/L (normal, 18.0–43.1), and the daytime GH profile measured using assay A was 9.6–14.0 mU/L. At 13 weeks gestation there was a decline of IGF-I to 33.9 nmol/L and in the daytime GH profile (assay A) to 5.4–6.8 mU/L. At 24 weeks, IGF-I had risen to 51.6 nmol/L. A simultaneous daytime GH profile at this time using assay A revealed levels between 21.3–22.1 mU/L, but only 2.1–3.0 mU/L with assay B. Assay A has significant cross-reactivity with human placental lactogen (HPL), unlike assay B. At 36 weeks, IGF-I was still elevated at 56.6 nmol/L, with a daytime GH profile of 16.6–17.7 mU/L using assay A and 1.5–3.9 mU/L with assay B. At 12 weeks postpartum, IGF-I was 71.4 nmol/L, and the daytime GH profile with assay B was 5.6–8.6 mU/L. These data support a picture of GH suppression during pregnancy in acromegaly associated with McCune-Albright syndrome, shown best with assay B, which discriminates between GH and HPL.

These results contrast with previous reports of pregnancy in uncontrolled acromegalics, in whom pituitary GH levels were unaffected by pregnancy, and total GH and IGF-I levels were noted to be elevated. These data suggest that GH secretion in a pregnant acromegalic with the McCune-Albright syndrome may not be entirely autonomous, as seen in classic acromegaly, but may be associated with a degree of negative feedback control that could be exerted by a circulating factor of placental origin, probably HPL or placental GH. (*J Clin Endocrinol Metab* **86:** 2456–2458, 2001)

THE MCCUNE-ALBRIGHT syndrome is characterized by a triad of clinical features, including polyostotic fibrous dysplasia, café au lait spots, and endocrinopathies (1, 2), such as acromegaly (3–7), Cushing's syndrome (8), hyperthyroidism (1, 9), prolactinomas (4, 5), and precocious puberty (9). The syndrome has been characterized at the molecular level as a gain of function mutation ($Arg^{201}His$ or $Arg^{201}Cys$) affecting exon 8 of the gene encoding the α-subunit of the G stimulatory protein ($G_s\alpha$), involved in the adenyl cyclase-cAMP pathway (10–12). Successful pregnancies in uncontrolled acromegaly have been reported together with GH and insulin-like growth factor I (IGF-I) profiles throughout the antenatal and postnatal periods (13). However, there have been no reports of pregnancy in an acromegalic with McCune-Albright syndrome associated with GH hypersecretion. Previous reports suggested that pathophysiological differences in GH hypersecretion exist between the two entities outside pregnancy (14). This report presents the endocrine data and obstetric outcome of a patient, with documented McCune-Albright syndrome and GH hypersecretion during pregnancy and the postpartum period.

Subject and Methods

A 36-yr-old Caucasian woman was studied who had presented with precocious puberty at 3 yr of age together with irregularly edged hyperpigmented (café au lait) macules and fibrous dysplasia, when a diagnosis of McCune-Albright syndrome was made (7). During her adolescence she had required multiple osteotomies with bone grafting to treat fibrous dysplasia in the left femur. At 25 yr of age, after facial surgery acromegaly was diagnosed after failure of GH suppression during an oral glucose tolerance test. The daytime GH profile ranged between 16.0–37.7 mU/L using assay A (see *Materials and Methods*). The corresponding IGF-I level was 146 nmol/L (age- and sex-matched normal range, 18.0–43.1 nmol/L). A high resolution computed tomography scan of the pituitary fossa with contrast enhancement showed a pituitary tumor with suprasellar extension together with thickened and diffuse vault sclerosis affecting the occipital and parietal bones (7). Transethmoidal surgery was attempted, but was abandoned because abnormal veins enveloped the enlarged pituitary, and the risk of potential hemorrhage was considered excessive. Pituitary irradiation of the tumor was performed by means of a three-field external beam irradiation therapy in fractionated doses; a total dose of 4500 rads was administered over 6 weeks. In the interim, octreotide treatment (100 μg, three times daily) was commenced. Two years post radiotherapy, daytime GH profile concentrations (assay A) remained elevated between 10–19 mU/L, with a corresponding IGF-I of 87.4 nmol/L.

Obstetric history

Despite receiving treatment for acromegaly, the patient failed to conceive after 4 yr of unprotected intercourse and regular periods. She was therefore referred to an assisted reproduction clinic with her partner, where a male cause of infertility was also identified. A management plan of stimulated reproductive cycles and artificial insemination with the husband's sperm was implemented, before which octreotide therapy was discontinued. Subsequently, she had two first trimester spontaneous abortions before the current pregnancy. The daytime GH profiles during pregnancy and at 12 weeks postpartum are illustrated in Table 1. No symptoms arose from her bony lesions during pregnancy, and she gave birth to a small full-term infant (birth weight, 2.5 kg) by sponta-

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TABLE 1. Day profiles of GH (milliunits per L) before, during, and after pregnancy in patient

Assay	0900 h	1000 h	1100 h	1200 h	1300 h	1400 h	1500 h	IGF-I (nmol/L)
Prepregnancy								
A	9.6	9.8	13.7	13.4	13.5	14.0	13.6	60.6
13 weeks								
A	6.4	5.4	5.6	6.5	6.4	6.8	6.7	33.9
24 weeks								
A	21.3	21.2	22.1	21.6	22.0	21.4	22.0	51.6
B	2.4	2.1	2.1	2.3	2.1	2.8	3.0	
36 weeks								
A	16.6	17.6	17.1	16.8	17.2	17.3	17.7	56.6
B	1.5	2.3	2.4	3.2	3.9	2.8	3.2	
Postpartum (12 weeks)								
B	5.6	7.7	5.6	7.9	8.0	8.0	8.6	71.4

Assay A, two-site immunoradiometric assay; significant cross-reaction with HPL. Assay B, two-site chemoluminescence immunoassay with no significant cross-reaction with HPL. IGF-I age related normal range, 18.0–43.1 nmol/L.

neous vaginal delivery. She remained normotensive, euglycemic, and euthyroid throughout pregnancy and the postpartum period. At 14 weeks postpartum, the patient commenced treatment with long-acting octreotide (10 mg daily, im). A high resolution pituitary computed tomography scan did not show any significant changes from previous imaging.

Materials and Methods

GH was measured by two assays. Assay A was a two-site immunoradiometric assay (IDS Ltd., Tyne and Wear, UK). The between-assay precision was 5.7% at a GH concentration of 27.7 mU/L and 5.7% at a GH concentration of 46.7 mU/L. There was significant cross-reactivity with human placental lactogen (HPL) in this assay, and the cross-reactivity of HPL at a concentration of 15,000 μg/L was 81%.

Assay B

GH was measured with a two-site chemiluminescence immunoassay kit (Nichols Institute Diagnostics, San Juan Capistrano, CA). The between-assay precision was 12.2% at a GH concentration of 24.3 mU/L and 11.1% at a GH concentration of 46.3 mU/L. There was no significant cross-reactivity in this assay with HPL, as addition of HPL at a concentration of 100,000 μg/L only increased GH by 0.05 μg/L. IGF-I was measured by RIA after acid extraction to reduce the interference from binding proteins (Biosource Technologies, Inc., Nivelles, Belgium). The between-assay precision was 11.7% at an IGF-I concentration of 21.9 nmol/L and 11.2% at an IGF-I concentration of 89.2 nmol/L.

Discussion

In the first trimester of a normal pregnancy GH is secreted in a pulsatile pattern, predominantly from the pituitary (15, 16). However, from about 17 weeks gestation, pituitary GH is steadily replaced by GH produced by the placenta (16–20). Thus, in normal pregnancy from the second trimester until delivery pituitary GH is suppressed, and IGF-I levels rise due to increased production of placental GH (21).

In active acromegaly pituitary GH levels are not significantly altered from the prepregnant state, suggesting that the adenomatous somatotrophs are not affected by inhibitory control of the factors that suppress pituitary GH secretion in normal pregnancy (13).

Our patient became pregnant while her McCune-Albright-associated acromegaly was active. However, in the first trimester there was a reduction in both IGF-I and GH levels resulting from a possible decrease in pituitary GH production during this period. In the second and third trimesters IGF-I levels rose again to prepregnancy levels; however, GH levels, measured to exclude significant interference from HPL (assay B), remained suppressed to nearly 2 mU/L (0.7 μg/L), which would be a desirable degree of GH suppression in the treatment of acromegaly (22, 23). After delivery, the daytime GH profile levels were significantly elevated, in keeping with uncontrolled acromegaly. The suppression of pituitary GH secretion may be due to a factor circulating in mid- to late pregnancy, which suppresses GH production while maintaining high IGF-I levels. This circulating factor may be placental GH or HPL. Placental GH is reported to rise in mid- to late pregnancy in normal and acromegalic pregnancies and is responsible for the corresponding rise in IGF-I levels (13, 21). We were unable to measure placental GH directly, but are aware of possible cross-reactivity of placental GH with assay B, the extent of which is not known. Therefore, the true values for pituitary GH levels over this period may be much lower. Our patient's data contrast with those described previously in acromegalic pregnancies by Beckers *et al.* (13), who found pituitary GH to be elevated during the entire pregnancy (13). HPL suppresses pituitary GH production normally in mid- to late pregnancy by a negative feedback mechanism (24, 25) and has also been shown to stimulate IGF-I production experimentally (26). The possible role of HPL, which increases from the second trimester to term, is supported by the extent of cross-reactivity with assay A.

Despite similarities, such as a failure of suppression of GH during a standard oral glucose tolerance test, GH hypersecretion in the McCune-Albright syndrome may show more pituitary radiological and pathological variations than acromegaly. The findings may be normal, consistent with hyperplasia, or, in 41% of cases, an adenoma (3, 4, 5, 14, 27). Our findings illustrate significant GH suppression in an acromegalic with the McCune-Albright syndrome during the second and third trimesters of pregnancy. This would suggest that GH secretion in this condition may not be entirely autonomous, but may differ from that which pertains in classic acromegalic pregnancies. We speculate that this could be a consequence of feedback control exerted by a circulating factor of placental origin, probably HPL or placental GH.

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